

Rare Functioning Pancreatic Endocrine Tumors

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Introduction

Pancreatic endocrine tumors (PETs) represent a heterogeneous group of tumors depending on functional status and histological differentiation. Functioning tumors are defined when clinical symptoms are related to peptide/hormone overproduction. Tumors secreting pancreatic polypeptide, human chronic gonadotrophin subunits, calcitonin, neurotensin or other peptides do not usually produce specific symptoms and should be considered as non-functioning tumors. In addition, it is important to note that several of these rare functioning tumors (RFTs) may have extra-pancreatic localizations such as VIPomas (10%), somatostatinoma (~50%), GRFoma (70%) and adrenocorticotrophic-secreting tumors (ACTHoma) (85%) [1].

Epidemiology and Clinicopathological Features

General

The incidence of clinically detected PETs has been reported to be 4–12 per million, which is much lower than that reported from autopsy series (about 1%) [2, 3]. Considering functioning PETs, insulinomas are the most common (17% incidence), followed by gastrinoma (15%). The remainder incorporates RFTs and includes: VIPoma (2%), glucagonoma (1%), carcinoid (1%), somatostatinoma (1%), and the rest are comprised of adrenocorticotrophic-secreting tumors (ACTHoma), GRFomas, calcitonin-producing tumors, parathyroid hormone-related peptide tumors, and other exceedingly rare neoplasms [4–14].

Similar to insulinomas and gastrinomas, the majority of RFTs are well-differentiated tumors [15]. Most RFTs present as malignant disease (WHO group 2) and liver metastases are common [8, 10, 14, 16, 17]. The 5-year survival rate is reported to be 60–100% for localized disease,

40% for regional disease, 29% for distant metastases, and 80% for all stages [2, 3]. In a publication from 1993 [18], the 5-year survival rate for advanced PETs approached 60 months from diagnosis. RFTs can occur at any age with an equal sex distribution [10, 14, 17]. Overall, about 15–30% of patients with PETs have multiple endocrine neoplasia type 1 (MEN-1). In MEN-1 patients, multiple tumors occur either synchronously or metachronously [19]. The incidence of MEN-1 in patients with RFTs is not known but in recent studies appears to be about 2% for VIPomas and glucagonomas [20, 21]; the incidence of MEN1 in somatostatinomas and GRFomas may be higher.

Patients with malignant tumors may present with mixed syndromes, or the tumors may change clinically over time.

Minimal Consensus Statements on Epidemiology and Clinicopathological Features – Specific

RFTs represent less than 10% of all PETs. The majority of patients with RFTs of the pancreas present with metastatic disease and only some with local disease. Most RFTs are diagnosed as WHO group 2. Not enough data in the literature is currently available to give accurate estimates on survival. The average age at diagnosis is estimated to be 50–55 years, with equal gender distribution. Patients with malignant tumors may present with mixed syndromes or tumors may change clinically over time. The most frequent familial condition associated with RFT is MEN-1.

Diagnostic Procedures: Imaging, Nuclear Medicine and Laboratory Tests

Diagnostic Procedures – General

The standard imaging procedures for RFTs, like other PETs, include endoscopic ultrasonography (EUS), contrast-enhanced helical CT or MRI of the abdomen (for both primary tumor and detection of metastases) in combination with somatostatin receptor scintigraphy (SRS). Image-fusion data, combining CT and SRS (SPECT), appears promising [22] in helping to accurately locate tumoral residues and plan surgery. EUS is a proven method in detecting most PETs and can be combined with EUS-FNA [23, 24]. SRS is a routine investigation for both primary tumors and metastases [25–27] and should be performed prior to treatment planning, especially surgery [68]. Gallium-labeled somatostatin analogue PET is also a promising detection method and despite the limited experience to date, the technique appears interesting, even

in the detection of small tumors [28, 29]. Standard PET with ^{18}F -glucose is not efficient in detecting well-differentiated tumors but may have some value in the detection of aggressive poorly differentiated PETs [30]. Recently, data using positron emission tomography with 5-HTP or ^{18}F -DOPA has also shown promising results and may be an option for the detection of small well-differentiated tumors [30–32].

Biological tests in the presence of RFTs should include both specific markers (VIP, glucagon, somatostatin, GRF, ACTH) and general markers (chromogranin A and pancreatic polypeptide) [14, 16, 17, 33, 34].

Minimal Consensus Statements on Diagnostic Procedures – Specific

Imaging and Nuclear Medicine

The combined use of CT scan (or MRI) and SRS is always recommended. Endosonography is not universally recommended as a first-line procedure in the investigation of RFT of the pancreas; it may be used in circumstances where CT, MRI and SRS are inconclusive, especially preoperatively; however, in patients with RFTs presenting with liver metastases, EUS is rarely necessary. Insufficient data is available to recommend PET methods on a routine basis and availability is limited. If certain circumstances in the suspicion of RFTs and all above recommended imaging are negative [68]. Gallium-labeled somatostatin analogues positron emission tomography may be performed; however, this is not universally available. Other examinations which may be useful are ^{18}F -DOPA-PET or ^{11}C -5-HTP PET (although availability and costs may have to be considered).

Laboratory Tests

The minimal biochemical work-up for RFTs includes specific biochemical analyses related to specific hormonal activity (example serum glucagon in suspicion of glucagonoma) and general markers chromogranin A and pancreatic polypeptide. Serum parathormone and calcium should also be performed as a baseline screening for MEN-1. All biochemical tests should be performed at first visit.

Pathology and Genetics

Histopathology and Genetics – General

Pathological diagnosis is mandatory in all cases and is easily obtained on tumor biopsy performed either in cases of hepatic metastases (e.g. ultrasound-guided biopsy) or of the primary tumor (preferably using EUS-FNA if locally-advanced, or at surgery). Pathological diagnosis of RFTs is performed using conventional HE staining, immunohistochemical staining with chromogranin and synaptophysin [15]. Determination of mitotic index by

counting 10 HPF and calculation of Ki-67 index by immunohistochemistry is mandatory [35]. The tumors should be classified according to WHO system knowing that the vast majority of RFTs fall within group 2 tumors. Genetic testing for hereditary tumor syndromes should be performed in case of suspected familial predisposition to MEN-1 or if the presence of other associated endocrinopathies (e.g. elevated serum calcium or PTH suggesting hyperparathyroidism and prolactinoma, respectively).

Minimal Consensus Statements on Histopathology and Genetics – Specific

Histopathology

Histology is always necessary to establish a diagnosis. Cytology may be helpful, but should be confirmed by histology. The minimal ancillary tests to support the histological diagnosis include immunohistochemistry for chromogranin A, synaptophysin and specific hormones according to the clinical setting. Both the mitotic count in 10 HPF (2 mm²) and the Ki-67 index (the latter performed using immunohistochemistry, although the techniques and counting standards need to be established) are mandatory in all cases. Immunohistochemistry for p53 and SSR2A receptors is not routinely recommended, with the exception of staining for SSR2A if SRS is not available.

Genetics

Germline DNA testing is only recommended in the presence of a positive family history of MEN-1, if there are suspicious clinical findings or if multiple tumors or precursor lesions are present. Genetic analysis should also be performed in suspected cases of MEN-1. Genetic testing, when performed, should include mutational screening and sequencing allowing the analysis of the entire coding gene and splice sites and genetic counseling should be sought prior to testing in all patients. Informed consent is mandatory prior to genetic testing. Somatic (tumor) DNA testing is not recommended.

Surgical and Cytoablative Therapies

Curative Surgery and Cytoablation – General

Indications for surgery depend on clinical symptoms, tumor size and location, malignancy and metastatic spread. Curative surgery should be sought also in metastatic disease, including ‘localized’ metastatic disease to the liver [36]. The type of surgery depends on the location of the primary tumor – pancreaticoduodenal resection (Whipple’s operation), distal pancreatectomy, tumor enucleation or enucleation in combination with resection. If malignancy is suspected, adequate lymph node clearance is mandatory.

In case of surgery for liver metastases, complete resection (RO) of metastases should always be considered both in functioning and non-functioning tumors. Liver surgery includes metastasis enucleation, segmental resection(s), hemihepatectomy or extended hemihepatectomy [37]. Intraoperative US should be performed for detection of all liver metastases. Prior to performing liver surgery, metastatic disease should be confined to the liver. Surgery should be undertaken only if 90% of the tumor mass can be successfully removed. Liver surgery can be done concomitantly with surgery of the primary tumor or on a separate occasion. In patients with RFTs, specific measures to avoid hormonal crisis are required during surgery (notably perioperative somatostatin analogue infusion) and specified anesthetic considerations [10]. Palliative surgery (to primary or metastases) may also be performed following multidisciplinary discussions and includes palliative or debulking resections (resection of >90% of tumor burden) to control symptoms related to hormonal hypersecretion [10, 14, 17, 33]. Bilateral adrenalectomy should be performed in selected cases with ACTH secretion resulting in Cushing syndrome [38, 39]. Liver transplantation may be indicated for a small number of patients, without extrahepatic metastases [40], in whom life-threatening hormonal symptoms persist despite maximal medical therapy and where standard surgery is not feasible.

Selective embolization alone or in combination with intra-arterial chemotherapy (chemoembolization – using streptozotocin, doxorubicin, mitomycin C, etc.) is an established procedure effective in controlling symptoms and controlling tumor progression [41]. Symptomatic responses of about 60% are reported with approximately a 40–50% tumor response [42–46]. It has not been established whether chemoembolization is more efficient than embolization alone. In experienced centers, the mortality rate is low, however, significant morbidity may occur (hepatic or renal failure). The postembolization syndrome is frequent with fever (sometimes prolonged), right upper quadrant pain, nausea, elevation of liver enzymes and a decrease in albumin and PT [41]. Adequate analgesia and hydration are recommended during and following treatment and prophylaxis with somatostatin analogues is always indicated when embolizing functioning tumors. Contraindications of TACE are complete portal vein thrombosis, hepatic insufficiency and a previous pancreaticoduodenectomy, which may expose the patient to severe complications of TACE.

Other local ablative methods which may be used alone or in combination with surgery, including radiofrequen-

cy ablation (RFA), cryotherapy and laser therapy [47–53]. Local ablative methods are usually reserved to treat limited disease (<8–10 metastases of <4–5 cm in diameter).

Minimal Consensus Statements on Surgery and Cytoablative Therapies – Specific

Curative surgery is always recommended whenever feasible after careful symptomatic control of the clinical syndrome [10]; the latter may be achieved by medical or locoregional treatments. Curative surgery should include oncological resection with lymphadenectomy. Surgery of liver metastases may be performed during treatment of the primary tumor. The best treatment option for liver metastases in RFTs is liver resection when feasible or chemoembolization. In patients with advanced stages, debulking surgical strategies have a major role. Liver transplantation may be reserved for rare circumstances in patients where extra-hepatic disease is ruled out. Bilateral adrenalectomy should be performed in selected cases with Cushing syndrome. Loco-regional ablative therapies recommended for the treatment of malignant RFTs of the pancreas include transarterial chemoembolization and radiofrequency ablation.

Medical Therapy

Medical Therapy – General

Both somatostatin analogues and interferon have been shown to be effective in the control of symptoms in functioning PETs [54] and this also includes RFTs [8, 10, 14]; in fact about 80–90% of patients with VIPoma and glucagonoma improve very promptly, overcoming diarrhea and skin rash, and 60–80% have a reduction in VIP and glucagon levels. Symptomatic relief is not always related to reduction in circulating hormone levels, indicating that somatostatin analogues have direct effects on the peripheral target organ. Escape from symptomatic control can be seen quite frequently but an increase in the dose of somatostatin analogues can help temporarily. The anti-tumor efficacy of somatostatin analogues appears less pronounced according to recent data, with objective tumor responses of <10% [55–58]; however, disease stabilization of up to 40% has been reported and these agents may be of value in subgroups of patients with slowly-progressive well-differentiated tumors expressing sst2 receptor subtype (i.e., a positive SRS) [56, 58]. In the control of symptoms, somatostatin analogue therapy should be initiated with short-acting substance (octreotide 100 µg subcutaneously ×2–3) for 1–2 days with titration according to clinical response. The patient can then be transferred to slow-release Lanreotide-SR® i.m., Lanreotide

autogel® s.c. or Sandostatin-LAR® i.m. (every 4 weeks) [59]. Likewise, interferon may be indicated in metastatic low-proliferating tumors and can be effective in VIPomas not responding to somatostatin analogs [60], but this requires confirmation in a controlled manner [56, 58].

Systemic chemotherapy is indicated in patients with metastatic and progressive RFTs using combinations of streptozotcin and 5-FU and or doxorubicin with objective response rates in the order of 35% [61, 62]. This is considerably lower than the 69% reported by Moertel et al. [63] in 1992. Chemotherapy in the adjuvant setting has not been explored to date. Peptide receptor radionuclide therapy (PRRT) has been made possible due to development of chelators suitable for radiometal labeling allowing for coupling of modified somatostatin analogues with trivalent metal ions (indium, gallium, yttrium, lutetium, etc.), thus allowing for further potential in diagnostic and therapeutic applications. Limited experience is available concerning PRRT in the treatment of RFTs; however, its efficacy in other advanced PETs with positive SRS has been demonstrated [64, 65].

Minimal Consensus Statements on Medical Therapy – Specific

Somatostatin analogues are an effective treatment in the control of symptoms in RFTs, especially in patients with VIPomas and glucagonomas. They may also be indicated as an antiproliferative treatment in selected cases based on positive SRS. Interferon may also be useful in selected patients with RFTs.

Systemic chemotherapy is reserved for patients with metastatic and progressive RFTs using streptozotocin plus 5-FU and or doxorubicin. Chemotherapy is not recommended in an adjuvant setting outside of a prospective evaluation. Peptide receptor radionuclide therapy can be used for RFTs in case of inoperable metastatic disease if the tumors have a high uptake (grade 3–4) on SRS.

Follow-Up

Follow-Up – General

As in other cases of PETs, follow-up in RFTs should include careful appraisal of clinical, biological and morphological parameters at regular intervals. No formal recommendation to date has been proposed. Given the high incidence of metastatic disease in RFTs, most patients are usually followed at intervals of between 3 and 6 months with appropriate biological and imaging tests.

Minimal Consensus Statements on Follow-Up – Specific

Follow-up for patients with RFTs should be at intervals of 3 to 6 months in metastatic disease and yearly in patients without metastatic disease. Following treatment, in patients with no evidence of residual disease, pertinent biochemical assessment (i.e. hormones known to be elevated prior to treatment, both specific and non-specific) should be initially performed and, when negative, further tests are not usually required. For patients with residual disease, specific markers coupled with CT-scan and SRS should be performed.

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